

## REMARKS

### *Interview Summary*

Applicant thanks the Examiner for the interview conducted on August 27, 2004, with inventor Dr. Szoka and Applicant's representative, Nathan Koenig. During the interview, details regarding the outstanding Office Action were discussed. Initially, Applicant discussed issues of indefiniteness regarding the phrase "amphipathic characteristic" and new matter issues regarding the deletion of the claim limitation that the orthoester directly attaches to an oxygen atom.

Next, the Nantz reference of record was discussed, with particular regard to the mechanisms of hydrolysis that are disclosed in that reference and their relevance to the orthoesters claimed by Applicant. Applicant believes that some agreement was reached with regard to the teachings of the Nantz reference, particularly in view of the amphipathic character of the compounds involved. Specifically, Applicant asserted that even if the R<sub>2</sub> group comprised an alkoxy, cleavage of that group would not undermine the amphipathic character of the compound. For example, the R<sub>1</sub> group is still hydrophobic and the hydrophilic headgroup R<sub>4</sub> are still connected to the compound, thus rendering it amphipathic. In contrast, Applicant asserted that both the diorthoesters and single orthoesters at issue in the application are no longer amphipathic after cleavage of the orthoester.

The interview was concluded with a discussion of possible ways to distinguish the Nantz reference more clearly. Applicant indicated an intention to file a response with amendments to more clearly distinguish Nantz.

### *Claim Rejections 35 USC 112*

The Examiner has rejected Claims 1, 2, 5- 7, 10-14 and 16 under 35 USC § 112, second paragraph, as being indefinite.

First, with respect to Claims 1, 2, 5 and 10-14, the Examiner states that it is unclear what was intended by the previous claim language "an ortho ester linker having an amphipathic characteristic." Applicant has amended the claim, and made corresponding amendments in the other independent claims, to clarify that it is the lipidic ortho ester conjugate, or composition as a whole, that has the amphipathic characteristic. Specifically, the claims all detail a hydrophobic portion joined to a hydrophilic portion by an ortho ester linker, thus forming an amphipathic

compound. This characteristic is an important feature of the claims, as hydrolysis of the pH sensitive ortho ester directly detaches the hydrophobic portion from the hydrophilic portion, eliminating the amphipathic characteristic. This has the functional significance of destabilizing any lipidic based encapsulator that was formed using the conjugates. Applicant respectfully submits that this amendment clarifies that it is not the ortho ester linker that has the amphipathic characteristic.

Next, with respect to Claim 16, Applicant has deleted the term "derivative" that was objected to by the Examiner.

In light of the above amendments and remarks, Applicants request that the Examiner withdraw the rejection of Claims 1, 2, 5- 7, 10-14 and 16 under 35 USC § 112, second paragraph.

The Examiner also rejected Claims 1, 2, 5- 7, 10-52 under 35 USC § 112, first paragraph, as failing to meet the written description requirements. With respect to Claims 1, 2, 5- 7 and 10-14, Applicant believes the amendment discussed above address the issue by clarifying that the lipid conjugate has the amphipathic, not the ortho ester linker itself.

With respect to the remaining independent claims, the Examiner states that the amendment in the previous response added new matter by deleting the requirement that the hydrophobic portion attach directly to an oxygen atom. This issue was discussed during the telephone interview, and Applicant believes that it was resolved. However, for the sake of completeness, Applicant respectfully submits that the claims as originally filed had no limitation regarding the attachment of the hydrophobic portion. Accordingly, the removal of this claim element does not add new matter, but rather returns to the scope of the claims to their original condition. Further, Applicant also respectfully submits that the limitation regarding the direct attachment of the hydrophobic portion to an oxygen atom did not successfully distinguish a prior art reference. Rather, this limitation was added in the response filed July 16, 2003 in an attempt to distinguish the Nantz reference. Applicant did assert that all the specific ortho esters disclosed in the specification shared that characteristic, however, the limitation was insufficient to distinguish Nantz. Therefore, Applicant has withdrawn the limitation as unnecessary, and introduces the present amendments to provide the distinction over Nantz.

Thus, Applicant requests that the Examiner withdraw the rejection of Claims 1, 2, 5- 7 and 10-52 under 35 USC § 112, first paragraph.

### *Claim Rejections 35 USC 102*

The Examiner has maintained the rejection of Claims 6, 7, 15, 16, 19-21, 24, 25, 30, 31, 34, 38, 39, 42 and 50-52 under 35 USC § 102(e) as anticipated by Nantz et al. The Examiner contends that the Nantz reference teaches lipid formulations having an ortho ester that could be used in conditions that would lead to hydrolysis of the ortho ester. The scope of this disclosure was discussed at length in the telephone interview referenced above. The Examiner's primary contention is that Nantz et al. discloses that R<sub>2</sub> of Formula I can be an alkoxy, which would represent an ortho ester linkage to R<sub>2</sub>. The Examiner concludes that this ortho ester could hydrolyze and cleave, thus releasing the remainder of R<sub>2</sub>, and releasing this hydrophobic portion from the rest of the molecule.

As discussed in the interview, Applicant submits that a key distinction over Nantz is that Nantz remains amphipathic in the situation suggested by the Examiner. Specifically, even if R<sub>2</sub> is an alkoxy and is released by hydrolysis of the resulting ortho ester linkage, R<sub>1</sub> and R<sub>4</sub> remain attached to the molecule. Since Nantz discloses that R<sub>1</sub> is hydrophobic and that R<sub>4</sub> is the hydrophilic head group, the molecule remains amphipathic after hydrolysis and cleavage of the R<sub>2</sub> group. In contrast, a fundamental concept of the invention is that hydrolysis of Applicant's ortho ester linkage separates the hydrophobic portion from the hydrophilic portion, thus eliminating the amphipathic character. In turn, this prevents the molecule from participating in a bilayer and destabilizes any encapsulator that incorporates it.

Applicant has amended the claims to emphasize this distinction. In particular, Claims 1, 19, 30, 38, 42, 48 and 50 have been amended to clarify that the molecule formed by the ortho ester linkage of a hydrophobic portion to a hydrophilic portion is amphipathic and that hydrolysis of the ortho ester necessarily eliminates the amphipathic characteristic. Applicant respectfully submits that this claim amendment fundamentally distinguishes Nantz and that none of the molecules disclosed by Nantz or suggested by the Examiner have an amphipathic characteristic that is eliminated by hydrolysis of an ortho ester linker.

For these reasons, Nantz et al. does not anticipate Claims 6, 7, 15, 16, 19-21, 24, 25, 30, 31, 34, 38, 39, 42 and 50-52 and Applicants respectfully request that the Examiner withdraw this 35 USC § 102(e) rejection.

### *Claim Rejections 35 USC 103*

The Examiner has rejected Claims 1, 2, 5, 6, 7, 10, 15, 16, 19-22, 24-32, 34-36, 38, 39, 42 and 50-52 under § 103(a) as being obvious over Zalipsky et al. in view of Nantz et al., Unger et al. and Unger et al. The only teaching of acid-labile ortho esters in this combination of references is from Nantz. Nantz, as discussed above, does not disclose or suggest the elimination of an amphipathic characteristic by cleavage of an ortho ester linker. Since neither the Zalipsky nor either Unger reference is directed to acid-labile ortho esters, they do not supply the teaching missing from Nantz. Therefore, Applicants respectfully request that the Examiner withdraw this §103 rejection of Claims 1, 2, 5, 6, 7, 10, 15, 16, 19-22, 24-32, 34-36, 38, 39, 42 and 50-52.

The Examiner also rejects Claims 19, 25, 30 and 35 under § 103(a) as being obvious over Nantz et al. in view of Huang et al. Again, Nantz et al. fail as a primary reference because they do not teach cleavage of an ortho ester linker eliminates an amphipathic characteristic. The Examiner has cited Huang et al. solely for the teaching of particular lipids that may be used to form liposomes. As such, Huang et al. do not compensate for the noted deficiencies of Nantz et al. Applicants thus request that the Examiner withdraw this §103 rejection of Claims 19, 25, 30 and 35.

Further, the Examiner has rejected Claims 19, 25, 30 and 35 under § 103(a) as being obvious over Nantz et al. in view of Sankaram et al. As discussed above, Nantz et al. fails as a primary reference because it does not teach cleavage of an ortho ester linker to eliminate an amphipathic characteristic. Sankaram et al. has been cited for the disclosure of particular liposomes, but does not suggest degradable ortho esters. As such, the reference does not compensate for the noted deficiencies of Nantz et al. Applicants thus request that the Examiner withdraw this §103 rejection of Claims 19, 25, 30 and 35.

The Examiner has also rejected Claims 19, 25, 30 and 35 under § 103(a) as being obvious over Nantz et al. in view of Sprott et al. Nantz et al., for the reasons discussed above, do not teach cleavage of an ortho ester linker that results in elimination of an amphipathic characteristic. Sprott et al. teaches only the use of Coenzyme Q, and thus, do not suggest the degradable ortho esters of the invention. As such, Sprott et al. do not compensate for Nantz et al.'s failure to suggest the claimed invention. Accordingly, Applicants respectfully request that the Examiner withdraw this §103 rejection of Claims 19, 25, 30 and 35.

Next, the Examiner has rejected Claims 1, 2, 5 and 6 under § 103(a) as being obvious over Zalipsky et al. in view of Nantz et al. and Haynes et al. The only teaching of acid-labile ortho esters in this combination of references is from Nantz. Nantz, as discussed above, does not disclose or suggest the invention because it does not teach cleavage of an ortho ester linker that eliminates an amphipathic characteristic. Since neither the Zalipsky nor the Haynes reference is directed to acid-labile ortho esters, they do not supply the teaching missing from Nantz. Therefore, Applicants respectfully request that the Examiner withdraw this §103 rejection of Claims 1, 2, 5 and 6.

Similarly, the Examiner has rejected Claims 1, 2, 5 and 6 under § 103(a) as being obvious over Zalipsky et al. in view of Nantz et al. and Sprott et al. The only difference is that the Examiner is citing Sprott for the teaching of coenzyme Q. Nevertheless, Nantz does not disclose or suggest the invention as discussed above. Further, neither the Zalipsky nor the Sprott reference is directed to acid-labile ortho esters so they do not supply the teaching missing from Nantz. Therefore, Applicants respectfully request that the Examiner withdraw this §103 rejection of Claims 1, 2, 5 and 6.

Next, the Examiner has rejected Claims 38 and 40 under § 103(a) as being obvious over Nantz et al. in view of Eppstein et al. As discussed above, Nantz et al. do not teach cleavage of an ortho ester linker that results in elimination of an amphipathic characteristic. Eppstein et al. is cited for the disclosure of powdered lipid formulations and this does not compensate for Nantz et al.'s failure to suggest the claimed invention. Accordingly, Applicants respectfully request that the Examiner withdraw this §103 rejection of Claims 38 and 40.

Similarly, the Examiner has also rejected Claims 38, 40 and 41 under § 103(a) as being obvious over Nantz et al. in view of Eppstein et al. and Lishko et al. The limitations of the Nantz reference are discussed above. Eppstein et al. is cited for the disclosure of powdered lipid formulations and Lishko for teaching lyophilization. These references do not compensate for Nantz et al.'s failure to suggest the claimed invention. Accordingly, Applicants respectfully request that the Examiner withdraw this §103 rejection of Claims 38, 40 and 41.

Finally, the Examiner has rejected Claims 42 and 45 under § 103(a) as being obvious over Nantz et al. in view of Needham et al. As discussed above, Nantz et al. do not teach cleavage of an ortho ester linker that results in elimination of an amphipathic characteristic. Needham et al. is cited for the disclosure of dry film compositions and thus does not compensate


for Nantz et al.'s failure to suggest the claimed invention. Accordingly, Applicants respectfully request that the Examiner withdraw this §103 rejection of Claims 42 and 45.

*Conclusion*

Based on the above remarks and amendments, Applicants submit that the pending claims are patentable and request their early allowance. To expedite prosecution, the Examiner may contact the Applicants representative Nathan Koenig at (541) 806-2252.

Respectfully submitted,

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